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CDK1 serves as a potential prognostic biomarker and target for lung cancer

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Abstract

Objective: Evidence from cell and mouse models and human tissues suggests that cyclin dependent kinase 1 (CDK1) is involved in lung cancer (LC) tumorigenesis. However, the different types of expression patterns and prognostic results of CDK1 need further analysis.

Methods: In the current study, we assessed CDK1 expression and LC patient outcomes using data from the Oncomine, GEPIA, and Kaplan–Meier Plotter databases. Additionally, mutations in the *CDK1* gene were analyzed by using the cBioPortal database. The expression of *CDK1* was verified by real-time quantitative PCR using the Human Protein Atlas database and human tissues.

Results: Expression of *CDK1* was higher in lung adenocarcinoma and squamous cell lung carcinoma tissues than in normal lung samples. Moreover, *CDK1* expression was linked to disease progression. Survival analysis indicated that upregulation of *CDK1* was related to poor overall survival, low first progression, and post-progression survival in patients with LC.

Conclusions: Our results indicate that CDK1 is a potential clinical target and prognostic biomarker for patients with LC.

Keywords

CDK1, expression, lung carcinoma, prognosis, survival, biomarker

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Introduction

Lung cancer (LC) is a frequently occurring malignancy and it accounts for a large proportion of cancer-related mortality worldwide.[1–3] It is categorized into small and non-small-cell subtypes in accordance with histology. The non-small-cell subtypes

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include large cell carcinomas, lung squamous cell carcinoma (LUSC), and lung adenocarcinoma (LUAD), which make up nearly 85% of all LC.[4] Despite considerable advancements in diagnosis and treatment, 5-year overall survival (OS) of LC patients remains below 15%.[5,6] Hence, prognostic markers and potential drug targets should be identified to enhance prognosis and individualized treatments.

Cyclin dependent kinases (CDKs) are serine/threonine kinases that regulate the cell cycle in cooperation with certain regulatory cyclins. CDK1 is the only essential CDK,[7,8] promoting the G_2/M and G_1/S transitions, as well as G_1 progression.[9] Unrestricted cell proliferation, an indicator of malignancy, is normally driven by alterations in CDK1 activity. Upregulation of CDK1 protein is closely related to the prognosis of several malignant tumors.[10] However, our understanding of the specific roles and potential mechanisms of CDK1 in lung cancer is limited. It has been reported that dysregulation of *CDK1* expression, which correlates with clinicopathological characteristics, is partially observed in humans but much remains to be discovered about the expression patterns and prognostic values of CDK1. In this study, we analyzed expression level and mutations of *CDK1* in patients with LC to determine potential gene and protein functions. We also aimed to assess the prognostic value of CDK1 in LC by analyzing information in published papers and in public gene expression databases.

Materials and methods

Ethical approval

The study was approved by the institutional review board (IRB) of Ningbo University (permit number: NO.89). This study was conducted according to the ethical guidelines of the Declaration of Helsinki. All datasets were retrieved from the published literature, so informed consent was not obtained.

Oncomine analysis

Oncomine (www.oncomine.org) is a public database of gene expression data in a variety of tumors. In this study, we used the Oncomine database to analyze the expression level of *CDK1* in lung cancer. The mRNA expression of *CDK1* in cancer specimens was compared with that in normal controls, using Student's *t*-test to determine significant differences. A *P*-value of 0.01 was used as the cut-off.

GEPIA database

GEPIA (http://gepia.cancer-pku.cn/) is an online database that incorporates gene expression data from The Cancer Genome Atlas (TCGA) and the Genotype Tissue Expression (GTEx) project, comprising 9,736 tumor samples and 8,587 normal controls. The GEPIA database allows users to explore gene expression as a function of cancer type or pathological stage. Additional functions include similar gene detection, correlation analysis, patient survival analysis, and dimensionality reduction analyses.[11] Using GEPIA, we analyzed the expression of *CDK1* in LC by tumor stage. The method for differential gene expression analysis was one-way ANOVA, using pathological stage as a variable for calculating differential expression. Then, we plotted $\log_2$ (TPM + 1) transformed expression data, where TPM is transcripts per million. GEPIA automatically generates violin plots of expression data based on patient pathological stage when we input *CDK1* gene.

RNA extraction and quantitative real-time PCR

To verify the mRNA expression of *CDK1*, we collected eight pairs of LC tissues

(LUAD and LUSC) and adjacent non-tumor tissues from the Department of Radiation Oncology, Ningbo Medical Center Lihuili Eastern Hospital from 1 January to 1 June 2019. Written informed consent was obtained from all participating patients. Approximately 20 mg of tissue was obtained from each sample for RNA extraction using Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocols. All PCR reactions were performed using an ABI Prism 5700 Sequence Detection System (PerkinElmer Applied Biosystems, Foster City, CA, USA). The primers and probes used for quantitative real-time PCR were as follows: *CDK1* forward primer: CCTAGCATCCCATGTCAAAAACTTG G; *CDK1* reverse primer: TGATTCAGTG CCATTTTGCCAGA; and *CDK1* probe: TGCTCTCGAAAATGTTAATCTATGA TCCAGCCAAACGA.

CCLE analysis

The mRNA level of *CDK1* in various cancers was determined in the Cancer Cell Line Encyclopedia (CCLE) database (https://portals.broadinstitute.org/ccle/home), which brings together sequencing data, chromosomal copy number, and gene expression from 947 human cancer cell lines.

Human Protein Atlas

The Human Protein Atlas (https://www.proteinatlas.org) contains immunohistochemical expression data for nearly 20 common types of tumors, and each tumor includes 12 individual tumor subtypes.[12] The database allows researchers to identify the expression patterns of certain proteins in tumors of a given type. In this study, we directly compared the expression level of CDK1 between tumor and normal tissues by immunohistochemistry.

Kaplan–Meier Plotter

The Kaplan–Meier (K-M) Plotter database was used to assess the prognostic relevance of CDK1 levels (www.kmplot.com).[13] This database includes gene expression and outcome data for 2,436 LC patients. The patients with LC were separated into two groups according to the median expression of CDK1 gene (high or low expression). The two patient cohorts were compared by K-M survival plots, and hazard ratios with 95% confidence intervals (CIs) and log rank *P*-values were calculated.

Functional and pathway enrichment analyses

Gene Ontology (GO) analysis identifies genes that are significantly overrepresented from three aspects: cellular component, molecular function, and biological process.[14] The Kyoto Encyclopedia of Genes and Genomes (KEGG) database is used to understand the high-level functions and utilities of a biological system.[15] The STRING database (https://string-db.org/) is used not only to construct a protein–protein interaction (PPI) network but also to provide a comprehensive functional approach by which to determine the biological meaning of genes. In this study, we performed GO function and KEGG pathway enrichment analyses of *CDK1* using the STRING database with a threshold of $P < 0.05$.

TCGA data and cBioPortal

TCGA compiles pathological and sequencing data from 30 different cancers.[16] Relevant data on lung adenocarcinoma and squamous cell carcinoma were included for further analyses of CDK1 using cBioPortal (https://www.cbioportal.org). Genomic profiles included mutations and putative copy-number alterations calculated using cBioPortal.

Statistical analysis

Data from the online databases were processed using the databases described above. Results derived from samples were analyzed by using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables between two groups were compared using Student's *t*-test. Differences with $P < 0.05$ were considered significant.

Results

Expression of CDK1 gene in LC

The Oncomine database was used to compare the expression of *CDK1* in LC and normal samples. The results showed that CDK1 was overexpressed in various cancers, and its expression was significantly increased ($P < 0.05$) in LC patients in 11 datasets (Figure 1a). We further queried

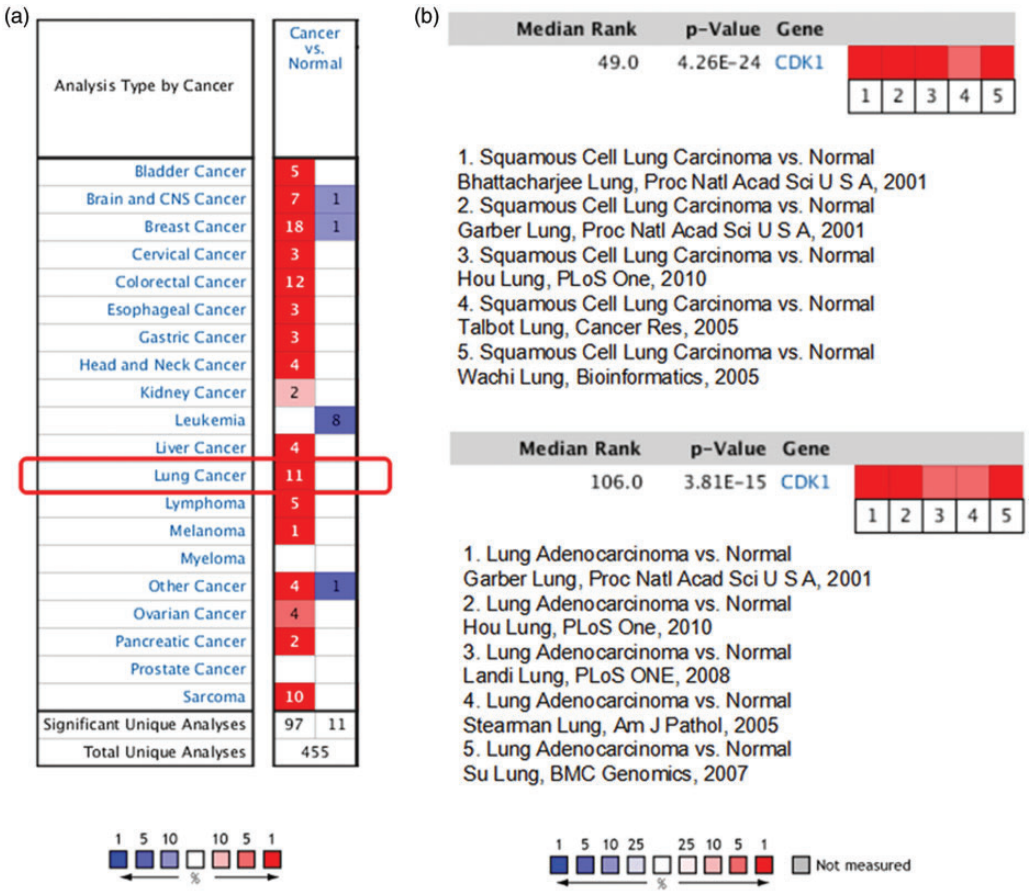

Figure 1. The transcription level of CDK1 in different types of cancers (Oncomine database; www.oncomine.org). (a) The graph presents the numbers of datasets with statistically significant mRNA upregulated (red) or downregulated expression (blue) of the target gene. The threshold was designed with following parameters: *P*-value of 1E-3 and fold change of 1.5. (b) The expression level of CDK1 was analyzed using the Oncomine database across several lung cancer studies. CDK1, cyclin dependent kinase 1.

the Oncomine database to analyze *CDK1* expression in several lung cancer studies. All results indicated that transcription levels of CDK1 in lung adenocarcinoma and squamous cell lung carcinoma were higher ($P < 0.05$) than those in normal lung tissues (Figure 1b).

Association between CDK1 expression and clinicopathological findings in LC patients

The expression level of *CDK1* between LC and normal lung tissues was compared by using the GEPIA database. The results indicated that expression of *CDK1* in LUAD and LUSC tissues was significantly higher ($P < 0.05$) than that in normal lung tissues (Figure 2a, b). We also analyzed expression of *CDK1* with tumor stage for lung adenocarcinoma and squamous cell lung carcinoma; expression of *CDK1* was positively and highly associated ($P < 0.05$) with advanced cancer stages (Figure 2c). After examining the mRNA expression pattern of *CDK1* in LC, we explored the protein expression pattern of CDK1 in LC by using the Human Protein Atlas. As shown in Figure 3a, CDK1 protein was not expressed in normal lung tissues, whereas high expression of CDK1 was observed in LC tissues. In addition, the results of CCLE analysis agreed with that of Oncomine, and suggested that CDK1 was notably upregulated ($P < 0.05$) in lung cancer cell lines (Figure 3b). To verify the mRNA expression level of *CDK1*, 8 pairs of LC tissues and adjacent non-tumor tissues were collected. The mRNA expression level of *CDK1* in LUSC and LUAD was significantly higher ($P < 0.05$) than that in normal tissues (Fig. S1). Taken together, our results showed that transcriptional and proteomic expression of CDK1 was upregulated in patients with LC.

CDK1 genetic alteration and its neighbor gene network in patients with LC

cBioPortal provides the frequency of alteration of *CDK1* mutations in LC. A total of 1097 patients with pulmonary cancer (TCGA, provisional) and lung squamous cell carcinoma (TCGA, provisional) were analyzed. Gene set/pathway was changed in 16 (1%) of the samples under queries. The percentage of genetic alterations was 1.6% based on the two LC datasets (Figure 4a). *CDK1* gene alteration was detected in 1.99% of 502 LUSC patients and 1.16% of 516 LUAD patients (Figure 4b). In addition, to better understand the relationship between CDK1 and LC, we analyzed protein–protein interactions. The PPI network was generated by STRING. and showed that SMC2, SMC4, NCAPG, CCNB2, NCAPH, BUB1, CCNB1, PLK1, BUB1B, CKS1B, MAD2L1, CDC20, CKS2, and CCNA2 were associated ($P < 0.05$) with CDK1 and its functions (Figure 4c).

Functional enrichment analysis of CDK1 in patients with LC

The functions of the *CDK1* gene were projected by analyzing GO and KEGG enrichment in the STRING database. GO enrichment analysis indicates how target host genes function in terms of biological mechanism, cellular components, and molecular functions. *CDK1* and associated genes were primarily enriched in mitotic chromosome condensation, G_2/M transition, mitotic cell cycle checkpoint, organelle organization, regulation of cell cycle, anaphase-promoting complex-dependent catabolic process, mitotic nuclear division, sister chromatid segregation, nuclear division, and cell division (Figure 5a). The molecular functions for these genes were mainly regulated by histone binding,

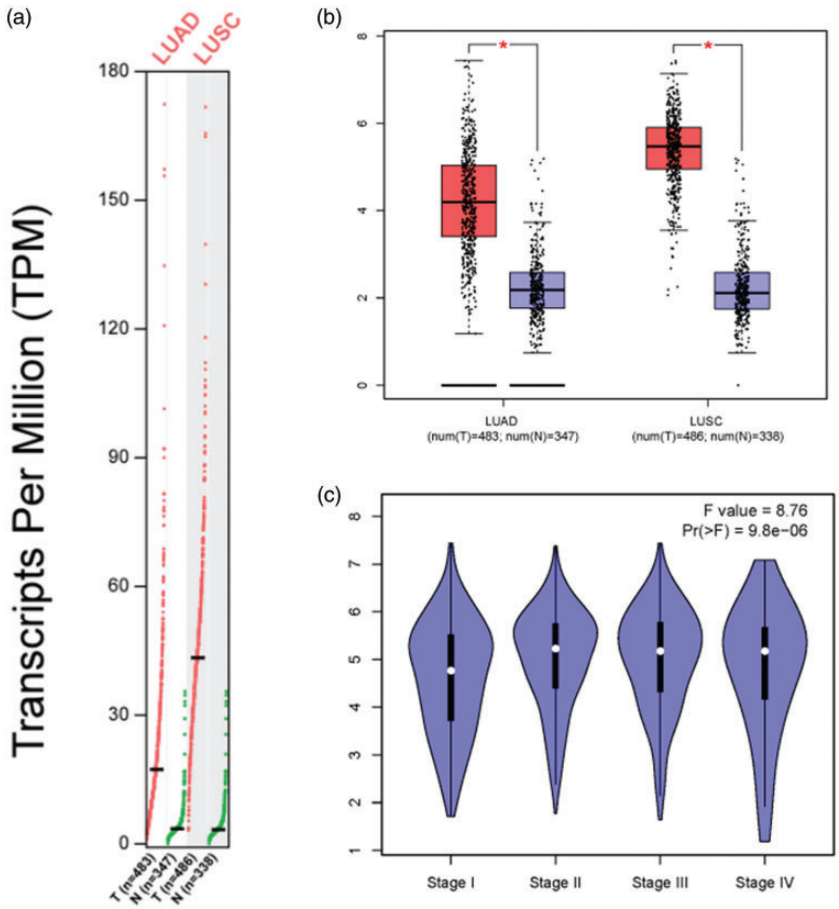

Figure 2. Correlation between *CDK1* expression and tumor stage in LC patients (GEPIA database; http://gepia.cancer-pku.cn/). (a) The expression profile of *CDK1* in LUAD and LUSC patients (GEPIA). (b) Box plots derived from gene expression data from GEPIA comparing the expression of *CDK1* in LC tissue and normal tissues; the *P*-value was set at 0.05. The abscissa indicates the cancer type and the ordinate indicates the expression level of *CDK1* (gene expression ~ disease). (c) Correlation between *CDK1* expression and tumor stage in LC patients (GEPIA). Violin plot derived from correlation between the expression of CDK1 and tumor stage in patients with LC; the *P*-value was set at 0.05. The abscissa indicates the stage of lung cancer and the ordinate indicates the expression level of *CDK1* (gene expression–pathological stage). CDK1, cyclin dependent kinase 1; LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

chromatin binding, single-stranded DNA binding, ubiquitin binding, enzyme activator activity, ATP binding, protein kinase binding, cyclin-dependent protein serine/threonine kinase activity, histone kinase activity, and protein serine/threonine kinase activity (Figure 5b). The cellular ingredients that these genes were involved in were cytoskeletal part, cyclin B1-CDK1 complex, microtubule cytoskeleton, nuclear lumen, cytosol, protein-containing complex, spindle, cyclin-dependent protein kinase holoenzyme complex, chromosomal part, and condensed chromosome

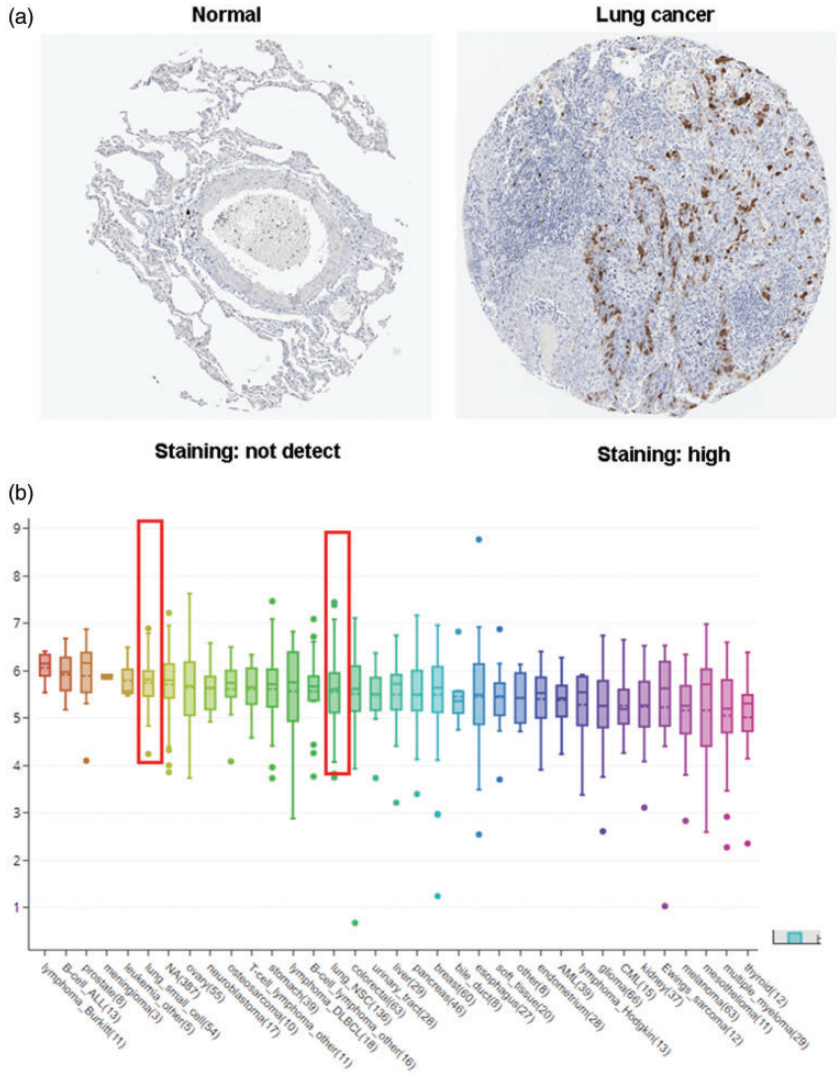

Figure 3. CDK1 was highly expressed in LC tissues and LC cell lines from Human Protein Atlas (https://www.proteinatlas.org) and CCLE (https://portals.broadinstitute.org/ccle) analysis. (a) CDK1 protein was not expressed in normal lung tissues (https://images.proteinatlas.org/3387/11302_A_2_4.jpg), whereas high expression was observed in LC tissues (https://images.proteinatlas.org/3799/10151_B_1_7.jpg). (b) CDK1 was overexpressed in lung cancer cell lines (shown in red frame). CDK1, cyclin dependent kinase 1; LC, lung cancer; CCLE, Cancer Cell Line Encyclopedia.

(Figure 5c). The KEGG pathways for CDK1 and neighboring genes are shown in Table 1. Among these pathways, the cell cycle, the p53 signaling pathway, pathways in small cell lung cancer, viral carcinogenesis, and the FOXO signaling pathway were involved in tumor development and pathogenesis of lung cancer.

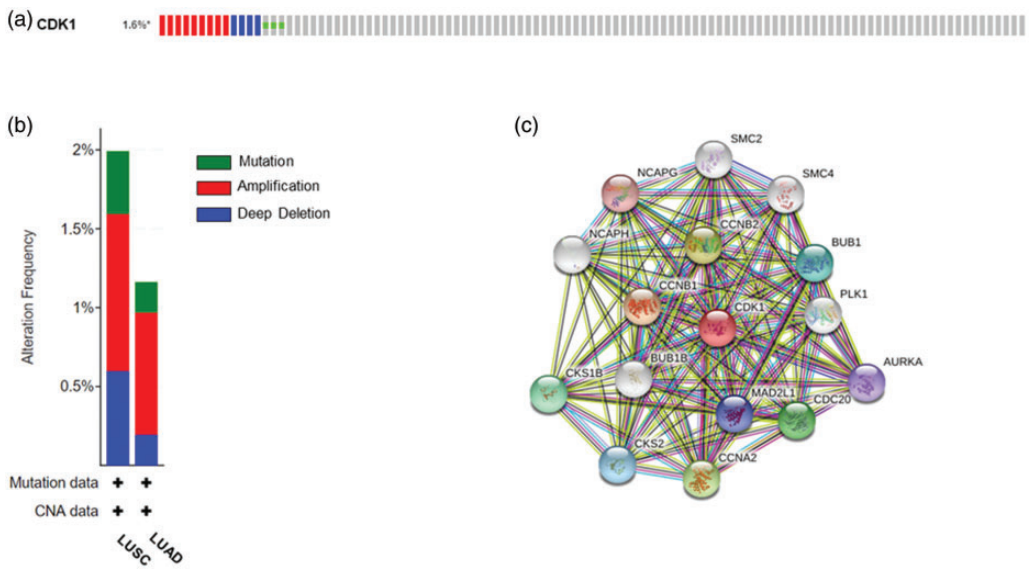

Figure 4. Alteration frequency of *CDK1* and neighbor gene network in LC (cBioPortal; https://www.cbioportal.org). (a) Summary of alterations in CDK1. (b) OncoPrint visual summary of alteration on a query of CDK1. (c) Protein–protein interaction network of CDK1. CDK1, cyclin dependent kinase 1; LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; CAN, copy-number alteration.

Correlation between CDK1 expression and survival of LC patients

We used K-M Plotter to analyze the prognostic value of mRNA expression of *CDK1* in LC patients. The results demonstrated a correlation for increased expression of *CDK1* with poor OS (Figure 6a), first progression (FP) (Figure 6b), and post-progression survival (PPS) (Figure 6c). These results indicated that mRNA expression of *CDK1* was significantly associated with prognosis in patients with LC, and CDK1 may be exploited as a useful biomarker for prediction of survival in LC patients.

Discussion

The cell cycle is an evolutionarily conserved process necessary for mammalian cell growth and development. Loss of normal cell-cycle control is a hallmark of human cancer.[17] Although a role for CDK1 in controlling the development and patient outcomes for several cancer types has been confirmed, further bioinformatics analysis of LC is still needed. In the current study, we determined mRNA expression and prognostic value (OS, FP, and PPS) of *CDK1* in LC. These results support efforts to improve LC diagnosis, prognostic analysis, and treatment.

The cell cycle is an essential and tightly controlled process regulating the proliferation and development of cells.[18] The loss of typical cell-cycle regulation indicates malignancy.[19] Many therapeutic approaches have been developed to regulate the cell cycle in cancers.[20] CDK1 is a catalytic subunit of a protein kinase complex, which induces cell entry into mitosis. This gene is responsible for controlling the transition from G_1 to S phase and from G_2 to M phase of the cell cycle.[8] Dysregulated activity of CDK1 has been observed frequently in cancers. CDK1 is reported to be an

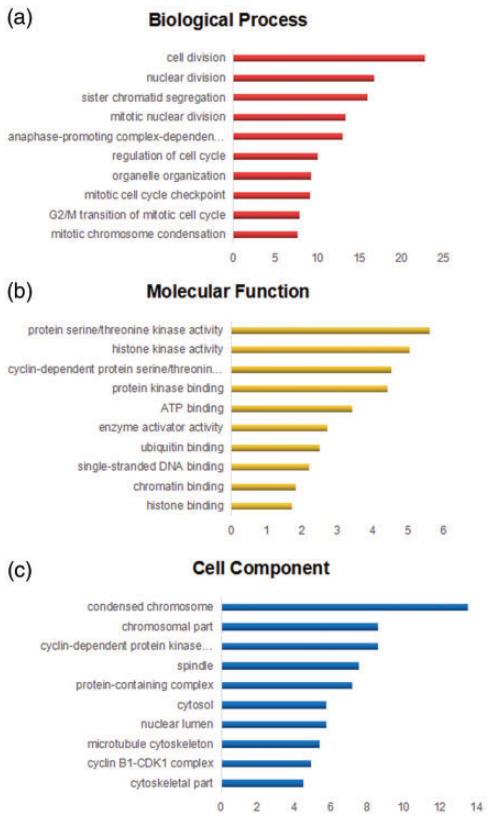

Figure 5. Functional enrichment analysis of CDK1 in patients with LC. Gene Ontology enrichment analysis predicted the functional roles of target host genes based on three aspects: (a) biological processes, (b) molecular functions, and (c) cellular components. CDK1, cyclin dependent kinase 1; LC, lung cancer.

adverse prognostic biomarker of LUAD, and increased expression of CDK1 is associated with a higher risk of cancer recurrence and poor survival compared with normal expression of CDK1 in patients with LUAD.[21] Another study demonstrated that using dinaciclib to inhibit the expression of CDK1 induced anaphase catastrophe in lung cancer.[22] These findings were similar to those of other studies, in which increased expression and activity of CDK1 were found in colorectal, prostate, and epithelial ovarian cancer.[23–25] In our study, findings from the Oncomine and GEPIA databases indicated that CDK1 upregulation was linked to clinical characteristics of patients with LC. Kaplan–Meier plots indicated that CDK1 levels were linked to poorer OS, FP, and PPS, in line with an oncogenic role for CDK1. These previously reported findings, together with those of our study, confirm that regulation of CDK1 is vital in governing the cell cycle and cell differentiation and that upregulation of CDK1 appears to contribute to lung cancer development and poorer differentiation. However, there are several limitations in our study. First, the data used in the current study were provided from various public databases, not generated by us. Second, the results were web-based and not verified by biological experiments.

Table 1. KEGG pathway analysis of CDK1 in lung cancer.

Pathway ID	Pathway name	Gene count	False discovery rate	Genes
04110	Cell cycle	9	4.07E-15	*BUB1*, *BUB1B*, *CCNA2*, *CCNB1*, *CCNB2*, *CDC20*, *CDK1*, *MAD2L1*, *PLK1*
04914	Progesterone-mediated oocyte maturation	8	4.33E-14	*AURKA*, *BUB1*, *CCNA2*, *CCNB1*, *CCNB2*, *CDK1*, *MAD2L1*, *PLK1*
04114	Oocyte meiosis	8	1.44E-13	*AURKA*, *BUB1*, *CCNB1*, *CCNB2*, *CDC20*, *CDK1*, *MAD2L1*, *PLK1*

(continued)

Table 1. Continued

Pathway ID	Pathway name	Gene count	False discovery rate	Genes
04218	Cellular senescence	4	3.08E-05	*CCNA2*, *CCNB1*, *CCNB2*, *CDK1*
04115	p53 signaling pathway	3	8.41E-05	*CCNB1*, *CCNB2*, *CDK1*
05166	HTLV-I infection	4	0.00013	*BUB1B*, *CCNB2*, *CDC20*, *MAD2L1*
04068	FoxO signaling pathway	3	0.00039	*CCNB1*, *CCNB2*, *PLK1*
05203	Viral carcinogenesis	3	0.00092	*CCNA2*, *CDC20*, *CDK1*
05222	Small cell lung cancer	2	0.0049	*CKS1B*, *CKS2*
05169	Epstein–Barr virus infection	2	0.0185	*CCNA2*, *CDK1*

KEGG, Kyoto Encyclopedia of Genes and Genomes; CDK1, cyclin dependent kinase 1.

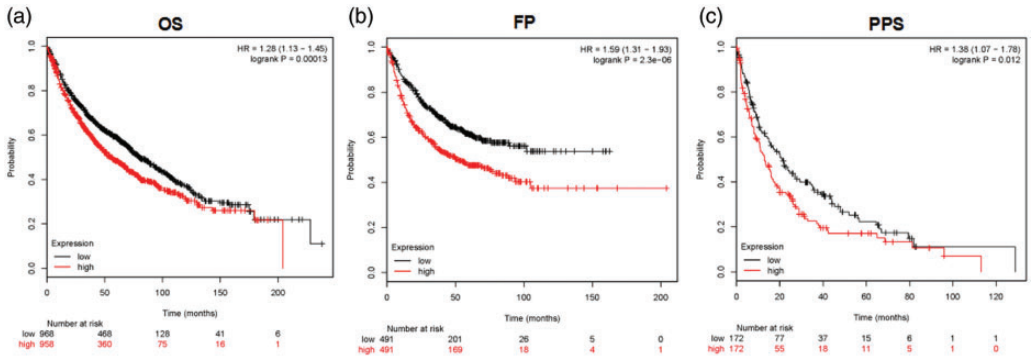

Figure 6. The prognostic value of expression level of CDK1 in LC patients (Kaplan–Meier Plotter; www.kmplot.com). The OS (a), FP (b), and PPS (c) survival curves comparing patients with high (red) and low (black) CDK1 expression in LC were plotted using the Kaplan–Meier Plotter database at a threshold *P*-value of < 0.05. CDK1, cyclin dependent kinase 1; LC, lung cancer; OS, overall survival; FP, first progression; PPS, post-progression survival; HR, hazard ratio.

Thus, further mechanistic studies based on our findings are needed.

In conclusion, our study provides a comprehensive bioinformatics analysis of CDK1, which may be involved in the progression and development of lung cancer. Our results may improve our understanding of the heterogeneity and complexity of LC. The increased expression of CDK1 in LC tissues may be important in LC oncogenesis, and CDK1 could become a prognostic marker. However, the mechanisms of CDK1 in LC and its value as a prognostic and therapeutic target need to be further studied.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Mingyao Li and Fenyi He conceived and designed the study strategy, acquired the data, performed the statistical analysis, and interpreted the data. Zhanchun Zhang collected

references and managed the data. Mingyao Li and Fenyi He drafted and revised the manuscript, Zhenfei Xiang wrote the manuscript, Danfei Hu prepared the figures, and all authors reviewed the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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